XANTHINE OXIDASE INACTIVATION ATTENUATES POSTOCCLUSION SHOCK AFTER DESCENDING THORACIC AORTA OCCLUSION AND REPERFUSION IN RABBITS

"Declamping shock" is observed after aortic crossclamping, with hypovolemia, hypotension, and metabolic acidemia invariably present. We hypothesized that oxidants derived from xanthine oxidase influence the resuscitative interventions required to maintain baseline hemodynamic and acid-base status after aortic occlusion and reperfusion in rabbits. We also hypothesized that inactivation of xanthine oxidase with sodium tungstate could reduce systemic injury as assessed by the release of lactate dehydrogenase and alkaline phosphatase. To test these hypotheses, we established aortic occlusion in rabbits (n = 10, standard diet; n = 8, tungstate diet) for 40 minutes by inflation of a 4F Fogarty catheter in the descending thoracic aorta followed by 2 hours of reperfusion. Sham-operated rabbits (n = 10, standard diet; n = 9, tungstate diet) served as controls. Tungstate-pretreated rabbits required significantly less Ringer's solution (28%), phenylephrine (68%), and sodium bicarbonate (30%) during reperfusion ($p < 0.005$). Lactate dehydrogenase and alkaline phosphatase release during reperfusion was significantly attenuated by tungstate pretreatment ($p < 0.05$). Tungstate pretreatment resulted in plasma xanthine oxidase activities significantly lower than those in the sham group administered a standard diet ($p = 0.007$). Resuscitation requirements and systemic injury were reduced by inactivation of xanthine oxidase in a rabbit model that simulates the situation of human thoracic aorta operations. (J THORAC CARDIOVASC SURG 1995;110:715-22)

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Cardiopulmonary, neurologic, and other organ injuries often occur after an otherwise uncomplicated descending thoracic aorta aneurysmectomy.[1] When such complications occur, they are often associated with a high rate of permanent organ dysfunction and death.[1] Reperfused (for example, spinal cord) and remote (for example, lung) organs commonly develop tissue edema after aortic crossclamping, a consequence of capillary membrane compromise. Whereas risk factors for multiple organ dysfunction in this setting include patient age[1] and concurrent organ dysfunction,[1, 2] the role of oxidants in mediating systemic injury may be of critical importance during reperfusion. The prevalence of paraplegia after descending thoracic aorta crossclamping in a dog model was reduced by administration of the enzymatic antioxidant superoxide dismutase (SOD).[3] Pulmonary oxidant injury was reduced by administration of the hydroxyl radical scavenger mannitol during abdominal aortic aneurysm repair.[4] A more immediate concern after aortic crossclamping is the pathologic condition of "declamping shock."[5-14] In addition to hypotension and hypovolemia,[5-11] patients may incur a metabolic acidosis during reperfusion that is refractory to treatment for several hours.[12-14] Oxidants play an important role in "declamping shock" as demonstrated by Casthely and associates.[7] These investigators reported an attenuation of the cardiovascular changes associated with descending thoracic aorta declamping in a dog model by infusion of SOD. The

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hepatocellular enzyme xanthine oxidase (XO) may be a source of oxidants in the setting of descending thoracic aorta declamping. We have observed that the resultant hepatic and intestinal ischemia-reperfusion that occurs after thoracic aorta occlusion and reperfusion in a rabbit model causes the systemic release of XO.[15]

The present study tested the hypothesis that inactivation of XO with tungstate will reduce the postocclusion shock associated with descending thoracic aorta occlusion and reperfusion in rabbits. The determination of the resuscitative interventions (Ringer's solution, phenylephrine, and sodium bicarbonate) required to maintain hemodynamic and acid-base status near preocclusion values during reperfusion served as a clinical assessment of postocclusion shock. The release of the ubiquitous cytosolic enzymes lactate dehydrogenase (LDH)[16] and alkaline phosphatase (ALP)[17] also served as a quantitative measure of systemic injury.

Methods

Surgical protocol. Male New Zealand white rabbits (Myrtle's Rabbits, Thompson Station, Tenn.) weighing 1.8 to 2.5 kg were randomly administered a standard diet or a molybdenum-deficient, tungstate-enriched diet (0.07% sodium tungstate, Purina Mills, St. Louis, Mo.) for 10 days before experimentation. A 10-day feeding period with a tungstate-enriched diet markedly reduces tissue xanthine dehydrogenase (XDH) plus XO (XDH+XO) activities as determined by Johnson, Rajagopalan, and Cohen.[18] Rabbits were anesthetized with intravenous fentanyl (Elkins-Sinn, Inc., Cherry Hill, N.J.) 100 μg/kg per hour and droperidol (American Reagent Laboratories, Shirley, N.Y.) 5 mg/kg per hour via a marginal ear vein. Arterial pressure was monitored by placement of a 22-gauge central ear artery catheter. After tracheostomy, mechanical ventilation (inspired oxygen fraction 1.0) with a Harvard Apparatus ventilator (model 661, Harvard Apparatus, Millis, Mass.) was done with arterial carbon dioxide tension maintained at 32 to 45 torr. Pancuronium bromide (Elkins-Sinn, Inc.) was administered at 0.1 mg/kg per hour intravenously to ensure relaxed chest wall muscle tone during ventilation. Central venous access was obtained via the right internal jugular vein with a 5F double-lumen catheter (Cook Critical Care, Bloomington, Ind.) for pressure monitoring and fluid administration. A right femoral arterial catheter was also placed to verify complete aortic occlusion in the aortic occlusion and reperfusion group. All rabbits received a maintenance infusion of Ringer's solution at 20 ml/kg per hour, and esophageal temperatures were maintained at 38° to 39° C with a heating pad.

Sham-operated animals (standard diet, $n = 10$; tungstate diet, $n = 9$) had the left femoral artery exposed, with sham thoracic aorta occlusion beginning with ligation of that artery. The aortic occlusion and reperfusion group (standard diet, $n = 10$; tungstate diet, $n = 8$) also underwent a left femoral cutdown, with insertion of a 4F Fogarty embolectomy catheter (American Edwards Laboratory, Irvine, Calif.) into the thoracic aorta with the balloon placed 1 to 2 cm above the diaphragm. Balloon position was predetermined by measuring the distance between the surface anatomy landmarks of the xiphoid process and the inguinal ligament. Catheter insertion to this length (usually 18 to 19 cm) at the inguinal ligament placed the balloon at the appropriate site as confirmed by postmortem examination. Thoracic aorta occlusion was achieved by inflation of the catheter balloon with up to 750 μl of saline solution. Subdiaphragmatic ischemia was confirmed by continuous monitoring of the femoral arterial pressure, which measured 0 to 10 torr during balloon inflation. After 40 minutes of occlusion, the balloon was deflated and the catheter removed from the aorta. The ensuing postocclusion shock was treated according to the algorithms given in the resuscitation protocol section, which follows. Blood samples were removed before induction of anesthesia, after 40 minutes of thoracic aorta occlusion, and at 5, 30, 60, and 120 minutes of reperfusion. Samples were taken from the ear or femoral artery. The blood was heparinized and centrifuged, with the plasma assayed as described in the biochemical analysis section, which follows. After 2 hours of reperfusion, the rabbits were killed with an overdose of pentobarbital (The Butler Company, Columbus, Ohio) of 65 mg/kg given intravenously.

Resuscitation protocol. Fluids and medications were administered with an Omni-Flow 4000 infusion pump system (Abbott Laboratories, North Chicago, Ill.).

Ringer's solution administration. Administration of Ringer's solution was increased during the last 20 minutes of aortic occlusion (120 ml/kg per hour). At the beginning of reperfusion, a bolus (20 ml/kg) was administered over 2 minutes and the infusion rate adjusted to maintain central venous pressure at the preocclusion value ±1 mm Hg. The cumulative dosage of Ringer's solution (in milliliters per kilogram) was determined at 15, 30, 60, and 120 minutes of reperfusion.

Phenylephrine administration. Phenylephrine (Elkins-Sinn, Inc.) administration began at reperfusion (10 mg/kg per hour) and was initially adjusted as follows: if the central venous pressure equalled the preocclusion value ±1 mm Hg and the mean arterial blood pressure was less than 85% of the value before occlusion, phenylephrine was administered. The rate of administration was continuously adjusted throughout reperfusion to maintain mean arterial pressure within the target range. The cumulative dosage of phenylephrine (in milligrams per kilogram) was determined at 15, 30, 60, and 120 minutes of reperfusion.

Sodium bicarbonate administration. Sodium bicarbonate 8.4% (Abbott Laboratories) was infused intravenously at 7 mEq/kg per hour during the last 20 minutes of aortic occlusion. An additional 5 mEq/kg was injected at reperfusion and the infusion continued at 7 mEq/kg per hour. The infusion of sodium bicarbonate was altered on the basis of arterial base excess (BE) changes as follows: if the BE was greater than 2, the infusion was decreased by 50%; if BE was less than 2 or greater than −2, no change; if BE was less than −2 but greater than −5, the infusion

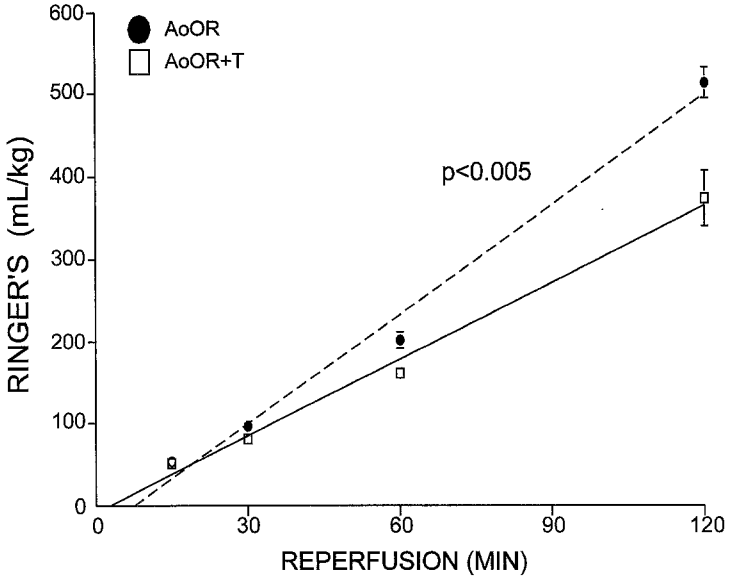

Fig. 1. Cumulative Ringer's solution requirement was significantly increased in aortic occlusion and reperfusion group administered standard diet *(AoOR)* as compared with that in aortic occlusion and reperfusion group pretreated with tungstate *(AoOR+T)*.

rate was increased 50%; if BE was less than −5, the infusion rate was increased 50% and a 1 mEq/kg bolus was administered. The total dosage (in milliequivalents per kilogram per 2 hours of reperfusion) was determined.

The study was approved by the Animal Review Committee of the University of Alabama at Birmingham. All animals received humane care in compliance with the "Principles of Laboratory Care" formulated by the National Society for Medical Research and with the "Guide for Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 809-23, revised 1978).

Biochemical analysis

LDH and ALP activity. Plasma LDH and ALP activities were determined on the day of experimentation. Plasma LDH was measured according to a modification of the procedure of Wacker, Ulmer, and Vallee.[19] Plasma ALP was determined according to a modification of the method of Tietz.[20]

XDH+XO. Plasma was stored at −85° C before analysis. Plasma samples were subjected to size exclusion chromatography with a G-25 column (Pharmacia, Piscataway, N.J.) to remove low-molecular-weight inhibitors of XDH+XO. Total plasma XDH+XO activity was determined by monitoring the production of uric acid in the presence of 75 μmol/L xanthine and 0.5 mmol/L oxidized nicotinamideadenine dinucleotide. Allopurinol (100 μmol/L), an inhibitor of XDH+XO, was used in parallel assay samples to confirm that urate formation was a result of XDH+XO activity. Oxonic acid (0.01 mmol/L) was added to inhibit uricase, an enzyme found in rabbits that oxidizes urate to allantoin, to prevent underestimation of XDH+XO activity. After 60 minutes of incubation at 37° C, the reaction was terminated by deproteinization. Deproteinized plasma was then assayed for uric acid with a high-performance liquid chromatography–based electrochemical technique developed by Tan and colleagues.[21]

Protein assay. Plasma and tissue samples were assayed for total protein concentration by a modification of the method of Smith and associates.[22] Values obtained were used to determine original plasma XDH+XO activities by comparison of precolumn and postcolumn sample protein concentrations.

Statistical analysis. All variables are expressed as mean plus or minus the standard error of the mean. The differences between the slopes of the regression lines in Figs. 1 and 2 (cumulative administration of Ringer's solution and phenylephrine) were compared by analysis of variance in which the hypothesis tested was the interaction of the group with time. Analysis of the total 2-hour cumulative dosage of all resuscitative interventions was conducted by a two-sample *t* test for independent samples with unequal variances. Analysis of the effect of ischemia-reperfusion on the release of circulating XDH+XO was conducted by repeated-measures analysis of variance. Comparison between groups for the change in plasma XDH+XO activity with each time point was done with use of the contrast statement of the repeated-measures analysis of variance. All analysis was done with SAS System for Personal Computers software, release 6.03 (SAS Institute, Cary, N.C.). An alpha error of <0.05 was considered significant.

Results

Sham-operated rabbits administered a standard or tungstate-enriched diet did not require any pharmacologic interventions during the operative pe-

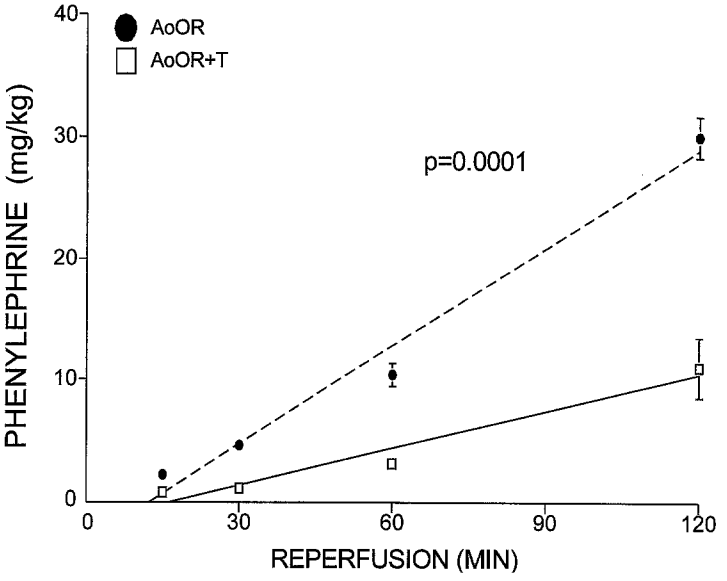

Fig. 2. Cumulative phenylephrine requirement was significantly decreased in aortic occlusion and reperfusion group pretreated with tungstate *(AoOR+T)* as compared with that in aortic occlusion and reperfusion group administered standard diet *(AoOR)*.

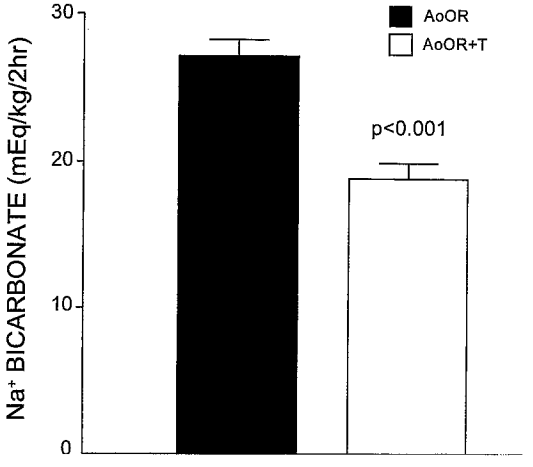

Fig. 3. Cumulative sodium bicarbonate requirement was significantly greater in aortic occlusion and reperfusion group administered standard diet *(AoOR)* as compared with that in aortic occlusion and reperfusion group pretreated with tungstate *(AoOR+T)*.

riod, with the exception of the infusion of maintenance fluids. Plasma LDH and ALP activities did not change significantly over time in sham-operated animals.

Ringer's solution administration (Fig. 1). The cumulative Ringer's solution requirement over time for rabbits in the aortic occlusion and reperfusion group pretreated with tungstate was significantly less during reperfusion as compared with that in those fed a standard diet ($p < 0.005$). The total dosage of Ringer's solution during the 2 hours of reperfusion was greater in the aortic occlusion and reperfusion group fed a standard diet (513 ± 19 ml/kg) than that in those administered tungstate (370 ± 33 ml/kg, $p < 0.005$).

Phenylephrine administration (Fig. 2). A marked reduction in cumulative phenylephrine requirements over time during reperfusion was observed in the rabbits pretreated with tungstate as compared with the requirement in those administered a standard diet ($p = 0.0001$). The total dosage of phenylephrine during the 2 hours of reperfusion was greater in the aortic occlusion and reperfusion group fed a standard diet (30 ± 1.6 mg/kg) than that in the group administered tungstate (9.75 ± 2.36 mg/kg, $p < 0.001$).

Sodium bicarbonate administration (Fig. 3). Rabbits administered a standard diet required significantly more sodium bicarbonate (27.1 ± 1.11 mEq/kg) during the 2 hours of reperfusion than animals pretreated with tungstate (18.9 ± 1.05 mEq/kg, $p < 0.001$).

LDH and ALP activity (Figs. 4 and 5). Plasma LDH and ALP activity did not increase during the ischemic period in the aortic occlusion and reperfusion groups. However, LDH and ALP activity increased significantly ($p < 0.05$) during reperfusion

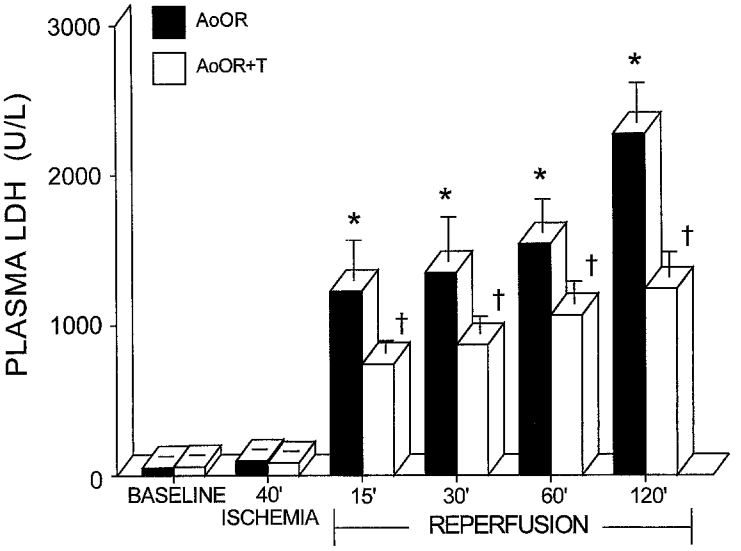

Fig. 4. LDH activity in plasma significantly increased during reperfusion in aortic occlusion and reperfusion group administered standard diet *(AoOR)* as compared with that in sham-operated rabbits ($*p < 0.05$). Pretreatment with tungstate significantly reduced plasma LDH activity in aortic occlusion and reperfusion group *(AoOR+T)* throughout 120 minutes of reperfusion ($\dagger p < 0.05$).

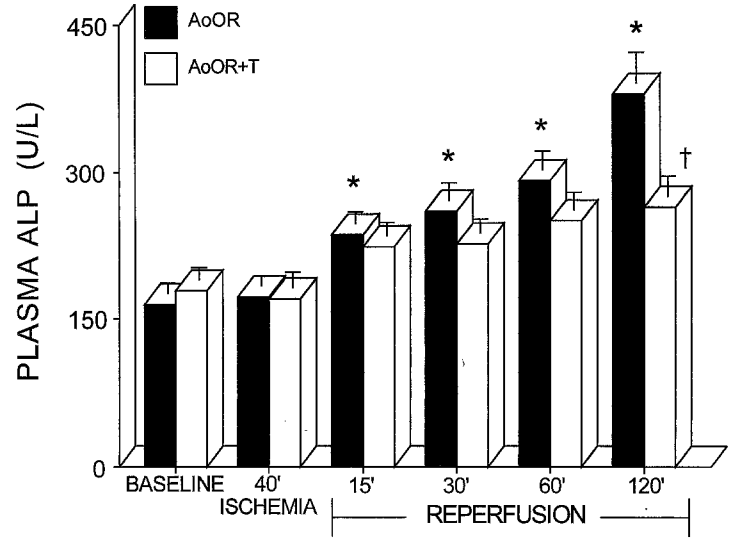

Fig. 5. ALP activity in plasma significantly increased during reperfusion in aortic occlusion and reperfusion group administered standard diet *(AoOR)* as compared with that in sham-operated rabbits ($*p < 0.05$). Pretreatment with tungstate significantly reduced plasma ALP activity in aortic occlusion and reperfusion group *(AoOR+T)* at 120 minutes of reperfusion ($\dagger p < 0.05$).

after thoracic aorta occlusion in both aortic occlusion and reperfusion groups as compared with values in the sham-operated rabbits. The tungstate-pretreated aortic occlusion and reperfusion group had significantly less LDH release throughout the reperfusion period as compared with values in the aortic occlusion and reperfusion group administered a standard diet ($p < 0.05$). Tungstate pretreatment significantly reduced ALP release at 2 hours of reperfusion ($p < 0.05$).

XDH+XO activity (Fig. 6). Plasma XDH+XO activity in the aortic occlusion and reperfusion group administered a standard diet was increased significantly from a baseline value of 36 ± 5.5 μU/ml

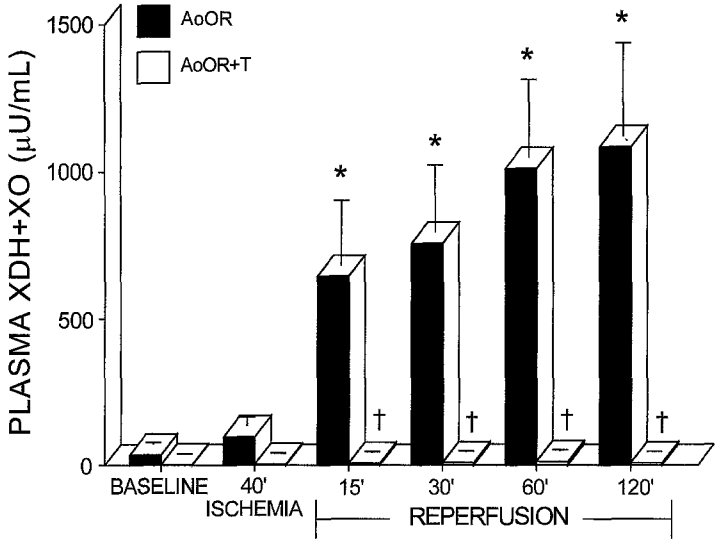

Fig. 6. XDH+XO activity in plasma significantly increased during reperfusion in aortic occlusion and reperfusion group administered standard diet *(AoOR)* as compared with that in sham-operated rabbits administered standard or tungstate-enriched diet (*$p < 0.05$). Pretreatment with tungstate significantly reduced XDH+XO activity in plasma of aortic occlusion and reperfusion group *(AoOR+T)* after descending thoracic aorta occlusion and reperfusion (†$p < 0.05$).

to 678 ± 213, 758 ± 229, 1011 ± 265, and 1085 ± 316 μU/ml (mean ± standard error of the mean) after 15, 30, 60, and 120 minutes of reperfusion, respectively ($p < 0.001$). Sham-operated animals pretreated with tungstate had significantly less plasma XDH+XO activity during experimentation than that observed in control animals administered a standard diet ($p = 0.007$).

Discussion

The concept that oxidants are involved in the pathophysiologic process of aortic declamping injury is controversial. Proposed mechanisms for the hemodynamic and metabolic disturbances observed after aortic declamping include vascular bed dilation in the ischemic area,[12] wash out of metabolic acids into the systemic circulation,[12, 14] release of a proteinaceous "vasodepressor factor,"[5] release of prostaglandin E,[6] and free radical–mediated capillary membrane compromise.[7] Casthely and colleagues[7] used a dog model of thoracic aorta crossclamping to demonstrate improved hemodynamic status during declamping by administration of SOD. In contrast, Vo, Dunbar, and Stanton[23] documented no beneficial hemodynamic effects in a dog model of hemorrhagic and declamping shock after administration of either allopurinol (XDH+XO inhibitor) or SOD. These conflicting observations can be resolved by examination of the different methods used in these studies. Casthely's group crossclamped the descending thoracic aorta for 1 hour and observed significant hemodynamic compromise at declamping in untreated animals. Vo's group occluded the distal abdominal aorta for 2 hours and reported minimal hemodynamic change at reperfusion in all experimental groups. If XO-derived oxidants contribute to declamping shock, one would expect to see a greater degree of hemodynamic aberration when tissues with high XDH+XO activity (such as liver and intestine) are reperfused, as was the case in the study by Casthely's group. Vo's group administered SOD (4 mg/kg) 15 minutes before reperfusion whereas Casthely's group infused SOD (15,000 U/kg) just before reperfusion. The administered dosages of SOD are not comparable, and the circulating half life of SOD is reported to be 8 minutes by Turrens, Crapo, and Freeman.[24] It is therefore likely that Casthely's group had a more efficacious SOD dosing regimen. Overall, the observations of both Casthely and colleagues[7] and the present study support the hypothesis that circulating oxidants play a significant role in the clinical manifestations of declamping shock after occlusion of the descending thoracic aorta.

The present study supports the concept that oxidants derived from circulating XDH+XO have a

significant impact on vasomotor tone during reperfusion. The in vitro findings of Gao, Korthvis, and Benoit[25] are in agreement with our in vivo data. Those investigators demonstrated that aortic rings had a significantly reduced contractile response to norepinephrine in the presence of XDH+XO and xanthine. Removal of endothelium from the aortic rings did not decrease the contractile dysfunction. Administration of the XDH+XO inhibitor oxypurinol prevented the loss of constrictor responsiveness. These data are consistent with our observations that inactivation of circulating XDH+XO significantly reduced phenylephrine and Ringer's solution requirements.

XO typically exists in an innocuous form (XDH) in nonischemic tissues, with purine catabolism occurring via reduction of nicotinamide-adenine dinucleotide.[26-30] However, if tissues are exposed to metabolic stress, such as hypoxia or ischemia, the enzyme converts to the oxidase form (XO) that can, in the presence of adequate substrate and molecular oxygen, generate the oxidants O_2^- and H_2O_2.[26-30] Molybdenum is essential for XDH+XO activity, and substitution with tungstate will inactivate XDH+XO tissue activity.[26] Under normal conditions XDH+XO is substrate-limited because purine levels in the systemic circulation are only 1 to 3 μmol/L.[28] Liver and intestine have the greatest tissue activity of XDH+XO[26-28] and vascular endothelial cells contain the enzyme to a lesser extent.[29, 30] In human studies, an increase in plasma XO activity has been documented during reperfusion of an upper extremity undergoing an orthopedic procedure.[31] Additionally, plasma concentrations of the XDH+XO substrates, hypoxanthine and xanthine, have been documented to increase after reconstructive aortic operation.[32, 33] It is therefore likely that XDH+XO and high concentrations of purine substrates could be released from reperfused hepatic and intestinal tissues after descending thoracic aorta crossclamping. Ultimately, free radical–mediated vascular endothelial cell injury could occur, leading to the clinical scenario of declamping shock and the release of cytosolic enzymes.

During reperfusion, conversion of XDH to XO in plasma occurs within seconds[28] by several mechanisms, including rapid and reversible oxidation of sulfhydryls or irreversible proteolysis.[29] Consequently, we report plasma activities as XDH+XO. Circulating XO, in the presence of elevated levels of plasma purines, could cause oxidant-mediated tissue injury. Endothelial cell injury may be further amplified by the release of chemoattractants and resultant neutrophil-mediated damage, as seen in other animal models.[34] Inactivation of XDH+XO reduced systemic injury after aortic occlusion and reperfusion in our rabbit model. A concurrent significant decrease in the release of ubiquitous cytosolic enzymes (LDH, ALP) and a reduction in sodium bicarbonate requirements was observed after tungstate pretreatment. These data suggest that XO plays a major role in the evolution of the oxidant-mediated microvascular injury that can ultimately lead to the scenario of multiple organ dysfunction often seen after thoracic aorta operations.

In conclusion, we present a clinically relevant rabbit model of thoracic aorta occlusion and reperfusion and document a reduction in resuscitative requirements and systemic injury after inactivation of circulating XDH+XO activity. Although sodium tungstate administration is not a clinically approved method of XDH+XO inactivation, a similar reduction in postocclusion shock and systemic injury may be realized by inhibition of circulating XDH+XO with clinically available medications (for example, allopurinol).

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